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PUBLIC HEALTH SERVICE REGULATIONS – BIOLOGICAL PRODUCTS

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Part 73 – Federal Control of the Sale, Barter, or Exchange of Biologic Products

and

Excerpts From Public Health Service Act.



U.S. Department of
HEALTH, EDUCATION, and WELFARE
Public Health Service

Public Health Service Publication No. 437

Revised June 1960

Formerly titled "Regulations of Biological Products"

This publication revises Public Health Service Publication No. 437: Regulations for the Sale, Barter, or Exchange of any Virus, Therapeutic Serum, Toxin, Antitoxin or Analogous Products, etc.

**From the Division of Biologics Standards
National Institutes of Health
Bethesda 14, Maryland**

REGULATION OF BIOLOGICAL PRODUCTS

**Revises Public Health Service
Publication No. 437**



U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

Division of Biologics Standards of the National Institutes of Health

INTRODUCTION

This publication contains an unofficial reprint of (a) excerpts from the Public Health Service Act, as amended (42 U. S. C. 201 et seq.), covering those portions primarily applicable to the control of biological products and of (b) the regulations pertaining to biological products adopted pursuant to such Act (42 C. F. R. Part 73), effective as of April 20, 1960.

Interstate shipment and the export or import of biological products were originally subject to Federal control under the provisions of the Act of July 1, 1902; 32 Stat. 728, 729. In enacting the Public Health Service Act, this authority was consolidated with other laws relating to the Public Health Service by the Act of July 1, 1944, entitled "An Act to consolidate and revise the laws relating to the Public Health Service, and for other purposes" (Public Law 410, 78th Congress; 58 Stat. 682). Title III, Part F of the Public Health Service Act is the part that relates directly to the control of biological products.

The Public Health Service Regulations consist of Title 42, Chapter I of the Code of Federal Regulations. This chapter was rearranged and reprinted in its entirety in the Federal Register of September 16, 1947, to integrate the numerous amendments and additions issuing since the original codification of Title 42 on June 1, 1938. The present publication includes Part 73, Biological Products, of these Regulations and includes amendments published in the Federal Register since September 16, 1947.

Reorganization Plan No. 1, 1953 (67 Stat. 631), transferred the Public Health Service to the Department of Health, Education, and Welfare, abolished the Federal Security Agency and the Office of Federal Security Administrator, and transferred all functions of the Administrator to the Secretary of the Department. The Plan was made effective April 11, 1953, by the Act of April 1, 1953 (Public Law 13, 83rd Congress, 67 Stat. 18). Accordingly, for all actions subsequent to April 10, 1953, the references in the statute and regulations to the terms "Federal Security Agency," "Federal Security Administrator," or "Administrator" have respectively been changed in this reprint to "Department of Health Education, and Welfare," "Secretary of the Department of Health, Education, and Welfare" and "Secretary."

EXCERPTS FROM THE PUBLIC HEALTH SERVICE ACT, As Amended

TITLE I—SHORT TITLE AND DEFINITIONS

SHORT TITLE

42 U. S. C., Note

SEC. 1. Titles I to VI inclusive, of this Act may be cited as the "Public Health Service Act."¹

DEFINITIONS

42 U. S. C. 201

SEC. 2. When used in this Act—

- (a) The term "Service" means the Public Health Service;
- (b) The term "Surgeon General" means the Surgeon General of the Public Health Service;
- (c) The term "Secretary" means the Secretary of the Department of Health, Education, and Welfare;
- (d) The term "regulations," except when otherwise specified, means rules and regulations made by the Surgeon General with the approval of the Secretary;
- (e) The term "executive department" means any executive department, agency, or independent establishment of the United States or any corporation wholly owned by the United States;
- (f) The term "State" means a State or the District of Columbia, Hawaii, Alaska, Puerto Rico, or the Virgin Islands, except that as used in section 361 (d)² such term means a State, the District of Columbia, or Alaska;
- (g) The term "possession" includes, among other possessions, Puerto Rico and the Virgin Islands.

TITLE II—ADMINISTRATION

PUBLIC HEALTH SERVICE

42 U. S. C. 202

SEC. 201. The Public Health Service in the Department of Health, Education, and Welfare shall be administered by the Surgeon General under the supervision and direction of the Secretary.

ORGANIZATION

42 U. S. C. 203

SEC. 202. The Service shall consist of (1) the Office of the Surgeon General, (2) the National Institutes³ of Health, (3) the Bureau of Medical Services, and (4) the Bureau of State Services. The Surgeon General is authorized and

¹Section 1 was amended by section 4 of the Hospital Survey and Construction Act to add Title VI to the original five titles of the Public Health Service Act.

²Relates to Part G—Quarantine and Inspection, Control of Communicable Diseases.

³Section 202 was amended by 6 (b) of the National Heart Act by adding an "s" to Institute.

directed to assign to the Office of the Surgeon General, to the National Institutes of Health, to the Bureau of Medical Services, and to the Bureau of State Services, respectively, the several functions of the Service, and to establish within them such divisions, sections, and other units as he may find necessary; and from time to time abolish, transfer and consolidate divisions, sections, and other units and assign their functions and personnel in such manner as he may find necessary for efficient operation of the Service. No division shall be established, abolished, or transferred, and no divisions shall be consolidated, except with the approval of the Secretary. The National Institutes of Health shall be administered as a part of the field service. The Surgeon General may delegate to any officer or employee of the Service such of his powers and duties under this Act, except the making of regulations, as he may deem necessary or expedient.

TITLE III—GENERAL POWERS AND DUTIES OF PUBLIC HEALTH SERVICE

PART F—BIOLOGICAL PRODUCTS

REGULATION OF BIOLOGICAL PRODUCTS

42 U. S. C. 262

SEC. 351. (a) No person shall sell, barter, or exchange, or offer for sale, barter, or exchange in the District of Columbia, or send, carry, or bring for sale, barter, or exchange from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession, any virus, therapeutic serum, toxin, antitoxin, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man, unless (1) such virus, serum, toxin, antitoxin, or other product has been propagated or manufactured and prepared at an establishment holding an unsuspended and unrevoked license, issued by the Secretary as hereinafter authorized, to propagate or manufacture, and prepare such virus, serum, toxin, antitoxin, or other product for sale in the District of Columbia, or for sending, bringing, or carrying from place to place aforesaid; and (2) each package of such virus, serum, toxin, antitoxin, or other product is plainly marked with the proper name of the article contained therein, the name, address, and license number of the manufacturer, and the date beyond which the contents cannot be expected beyond reasonable doubt to yield their specific results. The suspension or revocation of any license shall not prevent the sale, barter, or exchange of any virus, serum, toxin, antitoxin, or other product aforesaid which has been sold and delivered by the licensee prior to such suspension or revocation, unless the owner or custodian of such virus, serum, toxin, antitoxin, or other product aforesaid has been notified by the Secretary not to sell, barter, or exchange the same.

(b) No person shall falsely label or mark any package or container of any virus, serum, toxin, antitoxin, or other product aforesaid; nor alter any label or mark on any package or container of any virus, serum, toxin, antitoxin, or other product aforesaid so as to falsify such label or mark.

(c) Any officer, agent, or employee of the Department of Health, Education, and Welfare, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation of any virus, serum, toxin, antitoxin, or other product aforesaid for sale, barter, or exchange in the District of Columbia, or to be sent, carried, or brought from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession.

(d) Licenses for the maintenance of establishments for the propagation or manufacture and preparation of products described in subsection (a) of this section may be issued only upon a showing that the establishment and the products for which a license is desired meet standards, designed to insure the continued safety, purity, and potency of such products, prescribed in regulations, and licenses for new products may be issued only upon a showing that they meet such standards. All such licenses shall be issued, suspended, and revoked as prescribed by regulations, and all licenses issued for the maintenance of establishments for the propagation or manufacture and preparation, in any foreign country, of any such products for sale, barter, or exchange in any State or possession shall be issued upon condition that the licensees will permit the inspection of their establishments in accordance with subsection (c) of this section.

(e) No person shall interfere with any officer, agent, or employee of the Service in the performance of any duty imposed upon him by this section or by regulations made by authority thereof.

(f) Any person who shall violate, or aid or abet in violating, any of the provisions of this section shall be punished upon conviction by a fine not exceeding \$500 or by imprisonment not exceeding one year, or by both such fine and imprisonment, in the discretion of the court.

(g) Nothing contained in this Act shall be construed as in any way affecting, modifying, repealing, or superseding the provisions of the Federal Food, Drug, and Cosmetic Act (U. S. C., 1940 edition, title 21, ch. 9).

PREPARATION OF BIOLOGICAL PRODUCTS

42 U. S. C. 268

Sec. 352. (a) The Service may prepare for its own use any product described in section 351 and any product necessary to carrying out any of the purposes of section 301.

(b) The Service may prepare any product described in section 351 for the use of other Federal departments or agencies, and public or private agencies and individuals engaged in work in the field of medicine when such product is not available from establishments licensed under such section.

AUTHORITY: §§ 73.1 to 73.306 issued under sec. 215, 58 Stat. 690, as amended; 42 U.S.C. 216. Interpret or apply sec. 351, 58 Stat. 702; 42 U.S.C. 262. Other statutory provisions interpreted or applied are cited to text in parentheses.

CROSS REFERENCES: For Department of Health, Education, and Welfare regulations relating to drugs as defined in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.), see 21 CFR, Subchapter C. For exemption from section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) of new drugs licensed under the Public Health Service Act, see 21 CFR 130.2. For drugs intended solely for investigational use, see 21 CFR 1.114. For Bureau of Customs regulations relating to viruses, serums and toxins, see 19 CFR 12.21-12.23. For Post Office regulations relating to the admissibility to the United States mails see 39 CFR Parts 14 and 15, esp. § 15.(2).

DEFINITIONS

§ 73.1 Definitions.

As used in this part:

(a) "Act" means the Public Health Service Act (58 Stat. 682), approved July 1, 1944.

(b) "Secretary" means the Secretary of Health, Education, and Welfare.

(c) "Surgeon General" means the Surgeon General of the United States Public Health Service.

(d) "Institutes" means the National Institutes of Health in the Public Health Service.

(e) "Division of Biologics Standards" means the Division of Biologics Standards of the National Institutes of Health.

(f) "State" means a State or the District of Columbia, Puerto Rico, or the Virgin Islands.

(g) "Possession" includes among other possessions, Puerto Rico and the Virgin Islands.

(h) "Biological product" means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man:

(1) A virus is a product containing the minute living cause of an infectious disease.

(2) A therapeutic serum is the product obtained from the blood of an animal by removing the clot or clot components and the blood cells and intended for administration by a route other than ingestion.

(3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized.

(4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune.

(5) A product is analogous:

(i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.

(ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum and intended for administration by a route other than ingestion.

(iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, for the prevention, treatment, or cure of diseases or injuries of man through specific immunization.

(i) "Trivalent organic arsenicals" means arsphenamine and its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man.

(j) "Products" includes biological products and trivalent organic arsenicals. A product is deemed "applicable to the prevention, treatment or cure of diseases or injuries of man" irrespective of the mode of administration or application recommended, including use when

intended, through administration or application to a person, as an aid in diagnosis or in evaluating the degree of susceptibility or immunity possessed by a person, and including also any other use for purposes of diagnosis if the diagnostic substance so used is prepared from or with the aid of a biological product.

(k) "Proper name", as applied to a product, means the name designated in the license for use upon each container of the product.

(l) "Dating period" means the period beyond which the product cannot be expected beyond reasonable doubt to yield its specific results.

(m) "Expiration date" means the date of termination of the dating period.

(n) The word "standards" means specifications and procedures applicable to an establishment or to the manufacture or release of products, which are prescribed in this part and which are designed to insure the continued safety, purity and potency of such products.

(o) The word "continued" as applied to the safety, purity and potency of products is interpreted to apply to the dating period.

(p) The word "safety" is interpreted to apply to the relative freedom from harmful effect to the recipient when a product is prudently administered taking into consideration the character of the product in relation to the condition of the patient at the time.

(q) The word "sterility" is interpreted to mean freedom from viable contaminating microorganisms, as determined by the tests prescribed in § 73.73.

(r) The word "purity" is interpreted to mean the degree of freedom from extraneous matter, whether harmful to the recipient, deleterious to the product or otherwise, in the finished product.

(s) The word "potency" is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

(t) "Manufacturer" means any legal person or entity engaged in the manufacture of a product subject to license under the Act.

(u) "Manufacture" means all steps in propagation or manufacture and preparation of products and includes but is not limited to filling, testing, labeling, packaging, and storage by the manufacturer.

(v) "Location" includes all buildings, appurtenances, equipment and animals used, and personnel engaged by a manufacturer within a particular area designated by an address adequate for identification.

(w) "Establishment" includes all locations.

(x) "Lot" means that quantity of uniform material identified by the manufacturer as having been thoroughly mixed in a single container.

(y) "Selling agent" or "distributor" means any person engaged in the unrestricted distribution, other than by sale at retail, of products subject to license.

LICENSES: PROCEDURE

§ 73.2 Two forms of licenses.

There shall be two forms of licenses: establishment and product.

§ 73.3 Application for establishment and product licenses; procedure for filing.

To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Division of Biologics Standards, on forms prescribed for such purpose, and in the case of an application for a product license, shall submit data derived from laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity and potency, a full description of manufacturing methods, data establishing stability of the product through the dating period, sample(s) representative of the product to be sold, bartered or exchanged or offered, sent, carried or brought for sale, barter or exchange, summaries of results of tests performed on the lot(s) represented by the submitted sample(s), and specimens of the labels, enclosures and containers proposed to be used for the product. An

application for license shall not be considered as filed until all pertinent information and data shall have been received from the manufacturer by the Division of Biologics Standards.

§ 73.4 Establishment licenses; issuance and conditions.

(a) *Inspection—compliance with standards.* An establishment license shall be issued only after inspection of the establishment and upon a determination that the establishment complies with the applicable standards prescribed in the regulations in this part.

(b) *Availability of product; simultaneous request for and issuance of product license.* No establishment license shall be issued unless (1) a product intended for sale, barter or exchange or intended to be offered, sent, carried or brought for sale, barter or exchange is available for examination, (2) such product is available for inspection during all phases of manufacture and (3) a product license is requested and issued simultaneously with the establishment license.

(c) *One establishment license to cover all locations.* One establishment license shall be issued to cover all locations meeting the establishment standards.

§ 73.5 Product licenses; issuance and conditions.

(a) *Examination—compliance with standards.* A product license shall be issued only upon examination of the product and upon a determination that the product complies with the standards prescribed in the regulations in this part: *Provided*, That no product license shall be issued except upon a determination that the establishment complies with the establishment standards prescribed in the regulations contained in this part, applicable to the manufacture of such product.

(b) *Manufacturing process—impairment of assurances.* No product shall be licensed if any part of the process of or relating to the manufacture of such product, in the judgment of the Surgeon General, would impair the assurances of continued safety, purity and potency as provided by the regulations contained in this part.

§ 73.6 License forms.

(a) *Establishment license.* The establishment license form shall be prescribed by the Surgeon General and shall include:

(1) The name and address of the manufacturer.

(2) The name and address of the establishment.

(3) The names and addresses of all locations of the establishment.

(4) The license number.

(5) The date of issuance.

(b) *Product license.* The product license form shall be prescribed by the Surgeon General and shall include:

(1) The name and address of the manufacturer.

(2) The name and address of the establishment.

(3) The name and address of each location at which the product is manufactured.

(4) The license number of the establishment.

(5) The proper name of the product, with additional specifications, if any, which may be approved or required for additional labeling purposes.

§ 73.7 Changes to be reported.

Important changes in location, equipment, management and responsible personnel, or in manufacturing methods and labeling of any licensed product or of any product for which an application for a license is pending shall be immediately reported to the Director, Division of Biologics Standards, by any establishment holding a license, and, unless in case of an emergency, not less than 30 days in advance of the time such changes are made; failure to make such report shall constitute a ground for summary suspension of a license pending reinspection of the establishment or re-examination of the product.

§ 73.8 Products under development.

A biological product or trivalent organic arsenical undergoing development, but not yet ready for a product license, may be shipped or otherwise delivered from one State or possession into another State or possession provided such shipment or delivery is not for sale, barter

or exchange and is in accordance with section 505 of the Federal Food, Drug, and Cosmetic Act, as amended, and the regulations thereunder.

§ 73.9 Issuance, revocation or suspension.

A license shall be issued by the Secretary upon the recommendation of the Surgeon General and upon the determination by the Surgeon General that the establishment or the product, as the case may be, meets the standards established by the regulations in this part as herein prescribed or hereafter amended. Licenses shall be valid until suspended or revoked. An establishment or product license shall be revoked upon application of the manufacturer giving notice of intention to discontinue the manufacture of all products or of intention to discontinue the manufacture of a particular product for which a license is held. The Surgeon General shall recommend to the Secretary that a license be suspended or revoked whenever he finds, after notice and opportunity for hearing, that the establishment or any location thereof, or the product for which the license has been issued, fails to conform to the standards in the regulations in this part, as herein prescribed or as hereafter amended, designed to insure the continued safety, purity and potency of the manufactured product. In case of suspension, if the faulty condition is not corrected within 60 days or within such other period as may be specified in the notice of suspension, he shall recommend that the license be revoked. Except as provided in § 73.11, prior to the institution of proceedings looking to the suspension or revocation of a license the licensee shall be advised in writing of the facts or conduct which may warrant such action and shall be accorded opportunity within a reasonable period prescribed by the Surgeon General to demonstrate or achieve compliance with the regulations in this part.

§ 73.10 Licenses heretofore issued.

Any license heretofore issued and in effect upon the effective date of the regulations in this part shall remain in effect

unless and until superseded by a new license, or suspended or revoked, pursuant to the regulations in this part.

§ 73.11 Summary suspension.

Whenever the Surgeon General has reasonable ground to believe that an establishment or product for which a license has been issued fails to conform to the standards prescribed in the regulations in this part, and that by reason of such failure and of failure of the manufacturer to take prompt corrective measures on notice thereof, the distribution or sale of a licensed product would constitute a danger to health, or that the establishment and manufacturing methods have been so changed as to require in order to protect the public health a new showing that the establishment or product meets the standards prescribed in the regulations in this part, he may recommend to the Secretary that the license for the establishment or the product be summarily suspended and the manufacturer be required (a) to notify the selling agents and distributors to whom such product or products have been delivered of such suspension, (b) to furnish complete records of such deliveries and notice of suspension, and (c) to show cause within 60 days or such other period as may be specified in the order why the license should not be revoked.

§ 73.12 Review Board.

When deemed advisable by the Surgeon General, in matters involving the safety, purity and potency of licensed products or products for which an application for license is pending, the reports of inspection and laboratory examinations, together with any pertinent data the establishment may submit, shall be passed upon by a special board of three officers appointed by the Surgeon General for that purpose. The board shall report its findings to the Surgeon General who will forward its report, together with his findings and recommendations, to the Secretary.

§ 73.13 Opportunity for hearing.

Any manufacturer whose application for a license has been denied, or whose establishment or product license has been summarily suspended, without prior opportunity for hearing, may appeal from such denial or suspension and shall be entitled to a hearing thereon before a review body constituted as provided in § 73.12. The Surgeon General, upon review of the record, may affirm, reverse, or modify the findings of the review board, or may direct the taking of further testimony, and shall forward his determinations and recommendations to the Secretary.

§ 73.14 Suspension and revocation: publication.

Notice of suspension or revocation of license, with statement of cause therefor, may be published by the Secretary.

§ 73.15 Licenses; reissuance.

(a) *Compliance with standards.* An establishment or product license, previously suspended or revoked, whether upon application, or for failure to comply with standards or changes in standards prescribed in the regulations in this part, may be reissued or reinstated upon a showing of compliance with required standards and upon such inspection and examination as may be considered necessary by the Director of the Division of Biologics Standards.

(b) *Exclusion of noncomplying location.* An establishment or product license, excluding a location or locations that fail to comply with prescribed standards, may be issued without further application and concurrently with the suspension or revocation of the license for noncompliance at the excluded location or locations.

§ 73.16 Products in short supply; initial processing at other than licensed establishment.

Licenses issued to a manufacturer for an establishment shall authorize persons other than such manufacturer to conduct at places other than such establishment the initial, and partial processing of a product for shipment solely to such

manufacturer only to the extent that the names of such persons and places are registered with the Surgeon General and he finds, upon application of such manufacturer, that (a) the product is in short supply due either to the peculiar growth requirements of the organism involved or to the scarcity of the animal required for manufacturing purposes, and (b) such manufacturer has established with respect to such persons and places such procedures, inspections, tests or other arrangements as will assure full compliance with the applicable regulations of this part related to continued safety, purity and potency. Such persons and places shall be subject to all regulations of this part except §§ 73.2 to 73.15, 73.20 to 73.24, and 73.50 to 73.55. Failure of such manufacturer to maintain such procedures, inspections, tests or other arrangements, or failure of any person conducting such processing to comply with applicable regulations shall constitute a ground for summary suspension or revocation of the authority conferred pursuant to this section on the same basis as provided in §§ 73.11, 73.13 and 73.14 with respect to the summary suspension and the revocation of licenses.

FOREIGN ESTABLISHMENTS AND PRODUCTS**§ 73.20 Licenses required; products for controlled investigation only.**

Any biological or trivalent organic arsenical manufactured in any foreign country and intended for sale, barter or exchange shall be refused entry by collectors of customs unless manufactured in an establishment holding an unsuspended and unrevoked establishment license and license for the product. Unlicensed products which are not imported for sale, barter or exchange and which are intended solely for purposes of controlled investigation are admissible only if in accord with section 505 of the Federal Food, Drug, and Cosmetic Act, as amended, and the regulations thereunder.

§ 73.21 Procedure.

Except as otherwise provided in this part, licenses for foreign establishments and products shall be issued, suspended

or revoked in the same manner as licenses for domestic establishments and products. Each foreign establishment holding a license and consigning any licensed biological product or trivalent organic arsenical into any State or possession shall be required to file with the Surgeon General the name and address of any representative or representatives authorized by the establishment to distribute the product and such representative or representatives shall keep such records of such distribution as are required of domestic licensed establishments, and failure to maintain such records shall constitute ground for revocation of license.

§ 73.22 Form of license.

Licenses for establishments located in foreign countries shall be in form similar to that for domestic establishments except that they shall authorize manufacture for sending, carrying, or bringing for sale, barter or exchange from the foreign country designated in the license into any State or possession of the United States and shall specify that it is issued upon the condition that the licensee will permit the inspection during all reasonable hours of the establishment by any officer, agent, or employee of the Department of Health, Education, and Welfare authorized by the Secretary of the Department of Health, Education, and Welfare for such purpose.

§ 73.23 Smallpox vaccine; importation prohibited.

The importation of smallpox vaccine into any State or possession from any foreign country is prohibited except that smallpox vaccine may be sent from any foreign country, on containers indicating plainly the limited purpose intended, to the Director, Division of Biologics Standards, for test or research purposes or for vaccine manufacture.

§ 73.24 Samples to accompany each importation.

Each foreign importation of a biological product or trivalent organic arsenical from a licensed establishment, whether or not intended for investigational use

only, shall be accompanied by at least two final containers of each lot of any biological product and by at least 15 final containers of each lot of any trivalent organic arsenical contained in the shipment. Such samples shall be forwarded by the Collector of Customs at the port of entry to the Director, Division of Biologics Standards, for examination. If separate samples are not found accompanying the shipment, samples shall be obtained from the shipment by the Collector of Customs and forwarded to the Director, Division of Biologics Standards.

(Sec. 801, 52 Stat. 1058, as amended; 21 U.S.C. 381)

ESTABLISHMENT INSPECTION

§ 73.30 Inspectors.

Inspections shall be made by an officer of the Public Health Service having special knowledge of the methods used in the manufacture and control of products and designated for such purpose by the Surgeon General or by any officer, agent, or employee of the Department of Health, Education, and Welfare specifically designated for such purpose by the Secretary.

§ 73.31 Time of inspection.

The inspection of an establishment for which a license is pending need not be made until the establishment is in operation and is manufacturing the complete product for which a product license is desired. In case the license is denied following inspection for the original license, no reinspection need be made until assurance has been received that the faulty conditions which were the basis of the denial have been corrected. An inspection of each licensed establishment shall be made at least once each year. Inspections may be made with or without notice, and shall be made during regular business hours unless otherwise directed.

§ 73.32 Duties of inspector.

The inspector shall:

(a) Call upon the active head of the establishment, stating the object of his visit,

(b) Interrogate the proprietor or other

personnel of the establishment as he may deem necessary,

(c) Examine the details of location, construction, equipment and maintenance, including stables, barns, warehouses, manufacturing laboratories, bleeding clinics maintained for the collection of human blood, shipping rooms, record rooms, and any other structure or appliance used in any part of the manufacture of a product,

(d) Investigate as fully as he deems necessary the methods of propagation, processing, testing, storing, dispensing, recording, or other details of manufacture and distribution of each licensed product, or product for which a license has been requested, including observation of these processes in actual operation,

(e) Obtain and cause to be sent to the Director, Division of Biologics Standards, adequate samples for the examination of any product or ingredient used in its manufacture,

(f) Bring to the attention of the manufacturer any fault observed in the course of inspection in location, construction, manufacturing methods, or administration of, a licensed establishment which might lead to impairment of a product,

(g) Inspect and copy, as circumstances may require, any records required to be kept pursuant to § 73.36,

(h) Certify as to the condition of the establishment and of the manufacturing methods followed and makes recommendations as to action deemed appropriate with respect to any application for license or any license previously issued.

ESTABLISHMENT STANDARDS

§ 73.35 Responsible head.

A responsible person shall be in permanent and full control of the establishment in all matters relating to the manufacture of products. A responsible person is one who has been trained in the manufacturing techniques employed and the fundamental scientific facts upon which the manufacture of products rests, who is capable of enforcing discipline among the employees under his

supervision, and to whom sufficient authority has been delegated for such purpose.

§ 73.36 Records, samples, cultures.

(a) *Manufacturing and distribution records.* Records shall be made, concurrently with the performance, of the various steps in the manufacture, disposition, and distribution of each lot, so that at any time these steps as regards any lot number may be traced by an inspector. The records shall be retained, for such interval beyond the expiration date as is considered necessary for the individual product to permit the return of any clinical report of unfavorable reactions. This interval will vary with the type of product and its geographic distribution. A minimum of 6 months after the expiration date with 5 years as the extreme interval under all circumstances is considered adequate. Records of distribution of each lot shall in any event be kept as long as the lot remains the property of the licensed manufacturer.

(b) *Records of recall.* Complete records shall be maintained pertaining to the recall from distribution of any product upon notification from the Director, Division of Biologics Standards, of failure to conform with the standards prescribed in the regulations in this part, deterioration of the product or any other factor by reason of which the distribution of the product would constitute a danger to health.

(c) *Sterilization records.* Records including the date, duration, and temperature of each sterilization shall be made by means of automatic registering devices or under a system of recording which gives reasonable assurance of the accuracy and reliability of the record.

(d) *Animal necropsy records.* A necropsy record shall be kept on each animal from which a product has been obtained and which dies or is killed because of disease while employed in the manufacture of a product.

(e) *Retention of reference samples.* Reference samples from each lot shall be retained by the manufacturer until

the entire lot has become outdated and for 6 months thereafter. Exceptions may be authorized by the Director, Division of Biologics Standards, when the lot yields relatively few final containers and when such lots are manufactured by the same method in large numbers and in close succession.

(f) *Cultures.* Cultures and other materials while used in the manufacture of licensed products shall be labeled and preserved in a safe and orderly manner.

(g) *Records in case of divided manufacturing responsibility.* If two or more establishments participate in the manufacture of a product, the records of both establishments must show plainly the degree of responsibility of each in the manufacturing process.

§ 73.37 Physical establishment; construction, equipment and care.

(a) *Work with spore-bearing organisms.* All work with spore-bearing microorganisms shall be carried out in (1) an entirely separate building with its own entrance, or (2) a portion of a building used for the manufacture of other products constructed in such a manner as to be completely walled-off so that admission to the special unit may be gained only through an entrance independent of the remainder of the building. All containers used shall be permanently marked so as to avoid the possibility of contamination of products.

(b) *Work of a diagnostic nature.* Laboratory procedures of a clinical diagnostic nature involving possibly contaminated materials shall be in space set apart from that used for the manufacture of licensed products, except that manufacturing space which is used only occasionally may be used for diagnostic work provided spore-bearing pathogenic micro-organisms are not involved and provided the space is thoroughly cleaned before manufacturing is resumed.

(c) *Laboratory and bleeding rooms.* Laboratory rooms for the manufacture of licensed products, including the bleeding rooms and other places where cleanliness is essential, shall be efficiently screened and kept free of flies and other insects or vermin. Building construction shall be such as to insure freedom

from dust, smoke and deleterious or obnoxious odors in the laboratory and bleeding rooms and such as to permit thorough cleaning and, when necessary, chemical disinfection of bleeding rooms and rooms for smallpox vaccine animals.

(d) *Stables.* Stables shall be well lighted and well ventilated, and the floors shall be so constructed and cared for as to insure cleanliness.

(e) *Sterilization.* Sterilization equipment and methods used shall be such as to insure the complete destruction of contaminating, living organisms, including living spores. The containers, filling apparatus, and other pieces of apparatus or materials which may come in contact with biological products during manufacture shall be scrupulously clean. Such equipment shall be absolutely sterile unless the product is protected by subsequent sterilizing treatment.

(f) *Containers used in manufacturing.* All containers used in the manufacture of biological products shall be of such construction as will readily permit inspection for cleanliness.

(g) *Hot water available.* Hot water shall be provided in bleeding rooms and stables for smallpox vaccine animals.

(h) *Disposal of manure.* No manure shall be stored as to permit the breeding of flies on the premises nor shall the establishment be located in close proximity to off-property manure storage capable of engendering fly breeding.

(i) *Isolation of hog cholera manufacturing.* All personnel, animals and equipment used in the manufacture of hog cholera serum shall be kept entirely separate from personnel, animals, and materials used in the manufacture of biological products for human use.

§ 73.38 Animals used in manufacturing.

(a) *Quarantine and care.* Animals used in the manufacture of biological products shall be kept under competent daily inspection and preliminary quarantine for a period of at least 7 days before use. Only healthy animals free from communicable disease shall be used for manufacturing purposes and at all times shall be adequately housed, fed, and humanely treated. Particular care shall be taken during the quarantine period to

eliminate those animals of the equine genus which may be infected with glanders, and those of the bovine genus which may be infected with tuberculosis.

(b) *Immunization against tetanus.* All horses used in the manufacture of biological products, except those which are under active immunization for the manufacture of tetanus antitoxin, shall receive injections of tetanus toxoid in such amounts and at such intervals as experience has shown adequate to insure immunity to tetanus.

(c) *Disposal of used animals.* No animal used for the manufacturing of products shall be removed from the premises while it is capable of transmitting disease. An animal which is unsuitable because of its physical condition for the manufacturing of a product shall not be removed from the premises alive except for the purpose of being utilized for animal by-products. No animal shall be allowed to continue to live unnecessarily when to do so would be an inhumane act.

(d) *Reporting of certain diseases required.* In case of actual or suspected infection with foot and mouth disease, glanders, tetanus, anthrax, gas gangrene, equine infectious anemia, or equine encephalomyelitis among animals intended for use or used for the manufacture of biological products, the manufacturer shall immediately notify the Director, Division of Biologics Standards.

(e) *Smallpox vaccine production animals.* Animals used in the manufacture of smallpox vaccine shall be thoroughly cleaned with soap and water at the beginning of the quarantine and at its conclusion. No area of the animal shall be vaccinated which is liable to be contaminated by feces.

(f) *Treatment of vaccinated animals.* Preliminary to taking smallpox vaccine material from vaccinated animals, such animals shall be killed or rendered insensible to pain.

(g) *Restriction on attendants.* Personnel while caring for smallpox vaccine animals shall be excluded from horse stables and paddocks and from contact with horses.

STANDARDS FOR PRODUCTS: LABELS

§ 73.50 Container labels.

(a) The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

- (1) The proper name of the product;
- (2) Name, address, and license number of manufacturer;
- (3) Lot number;
- (4) The expiration date.

(b) If the final container is capable of bearing only a partial label, the final container shall show as a minimum the name (expressed either as the proper or common name), the lot number, and the name of the manufacturer and, if the final container is incapable of bearing any label, the items shall appear only on the outside label.

(c) If the final container is a multiple dose container, the container label must indicate the recommended dose. When the label has been affixed to the container a sufficient area of the container must remain uncovered for its full length or circumference to permit inspection of the contents.

§ 73.51 Proper name on outside label.

The proper name in the form designated in the product license for such purpose must appear upon the outside label in legible type and shall be given precedence in position and prominence over any trade-mark or trade name used:

(a) The "outside label" is the label of the carton enclosing one or more final containers, except that if no such carton is used the label of the individual final container is regarded as the outside label.

(b) "Legible type" includes only type of a size and character which can be read with ease when held in a good light and with normal vision.

(c) "Precedence in position" of the proper name will have been observed if it is placed above any trade-mark or trade name and provided it is symmetrically arranged with respect to other printing on the label.

(d) "Precedence in prominence" of the proper name will have been observed if

the style of type is of the same or greater point size and of equal face, or heavier, than that used in printing the trade-mark or trade name, and if the contrast in color value between the proper name and the background is not less than that between the trade-mark or trade name and the background.

§ 73.52 Outside label; additional items.

The label affixed to the outside carton shall include, in addition to the proper name and the items required on the label of the final container, the following:

(a) The preservative used and its concentration,

(b) The volume of the contents, if a liquid, or the weight, if a solid, and the potency or dosage if more than one strength is dispensed,

(c) The recommended storage temperature,

(d) The words "Shake Well," or equivalent, when indicated by the character of the product,

(e) The dose and route of administration recommended or reference to such directions in an enclosed circular,

(f) The source of the product when a factor in safe administration,

(g) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no standard of potency has been prescribed, the words "No U.S. standard of potency."

§ 73.53 Divided manufacturing responsibility to be shown.

If two or more establishments participate in the manufacturing process, the name, address, and license number of each must appear on the label of the final container, if capable of bearing a full label, and on the outside label.

§ 73.54 Name of selling agent or distributor.

The name and address of the selling agent or distributor of a product may appear on the label under the designation of "selling agent" or "distributor" provided that the name and address of the manufacturer is given precedence in prominence.

§ 73.55 Products for export.

Labels on packages or containers of products for export may be adapted to meet specific requirements of the regulations of the country to which the product is to be exported provided that in all such cases the minimum label requirements prescribed in § 73.50 are observed.

STANDARDS FOR PRODUCTS: GENERAL

§ 73.70 Tests prior to release required for each lot.

No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product. Each applicable test shall be made on each lot after completion of all processes of manufacture which may affect compliance with the standard to which the test applies.

§ 73.71 Potency.

Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency in a manner adequate to satisfy the interpretation of potency given by the definition in § 73.1(s).

§ 73.72 Identity and safety.

(a) The contents of a final container of each filling of each lot shall be tested for identity and for safety either after the labels have been affixed to the final container or affixed, both outside and inside, to the multiple container storage receptacle just prior to its sealing for storage purposes, except that exceptions to this procedure may be authorized by the Director, Division of Biologics Standards, to apply when the volume of the final container is very large and when more than one lot is processed each day.

(b) The identity test shall be specific for each product in a manner which will adequately identify it and distinguish it from any other product being processed in the same laboratory. In general, identity may be established either through the physical or chemical characteristics of the product, inspection by

macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests.

(c) In general, the safety test shall consist of the parenteral injection of the maximum volume tolerated, but not more than 0.5 ml. into mice weighing approximately 20 grams each and 5.0 ml. into guinea pigs weighing approximately 350 grams each. When the injections are made into at least two animals of each species, there shall result neither significant symptoms nor death during an observation period of not less than 7 days. Variations from this test, either in the volume injected or in the species of test animal used shall be made whenever required because of the human dose level demanded of the product or because of any individual demands of the product itself.

§ 73.73 Sterility.^{1/}

Except as provided in paragraph (f), the sterility of each lot of each product shall be demonstrated by the performance of the tests prescribed in paragraphs (a) and (b) of this section for both bulk and final container material. Bulk material shall be tested separately from final container material and material from each final container shall be tested in individual test vessels.

(a) *The test*—(1) *Using Fluid Thioglycollate Medium.* The volume of product, as required by paragraph (d) of this section (hereinafter referred to also as the "inoculum"), from samples of both bulk and final container material, shall be inoculated into test vessels of Fluid Thioglycollate Medium. The inoculum and medium shall be mixed thoroughly and incubated at a temperature of 30° to 32° C. for a test period of no less than seven days and examined visually for evidence of growth on the third, fourth or fifth day and on the seventh or eighth day. If incubation is continued beyond eight days, an additional examination shall be made on the last day of the test period. If the inoculum renders the medium turbid so that the absence of growth cannot be determined reliably by visual examination, portions of this turbid medium in amounts of no less

than 1.0 ml. shall be transferred on the third, fourth or fifth day of incubation, from each of the test vessels and inoculated into additional vessels of medium. The material in the additional vessels shall be incubated at a temperature of 30° to 32° C. for no less than seven days. Notwithstanding such transfer of material, examination of the original vessels shall be continued as prescribed above. The additional test vessels shall be examined visually for evidence of growth on the third, fourth or fifth day of incubation and on the seventh or eighth day and if incubation is continued beyond a period of eight days, an additional examination shall be made on the last day of the incubation period. If growth appears, repeat tests may be performed as prescribed in paragraph (b) of this section and interpreted as specified in paragraph (c) of this section.

(2) *Using Fluid Sabouraud Medium.* Except for dried products, a test for fungi and yeast shall be made on final container material, following the procedures prescribed in subparagraph (1) of this paragraph except that (i) the medium shall be Fluid Sabouraud Medium; (ii) the incubation shall be at a temperature of 20° to 25° C.; (iii) the period of incubation shall be no less than 10 days and an examination shall be made on the tenth or eleventh day in lieu of an examination on the seventh or eighth day.

(b) *Repeat tests*—(1) *Repeat bulk test.* If growth appears in the test of the bulk material, the test may be repeated to rule out faulty test procedures by testing at least the same volume of material.

(2) *First repeat final container test.* If growth appears in any test (thioglycollate or Sabouraud) of final container material, that test may be repeated to rule out faulty test procedures by testing material from a sample of at least the same number of final containers.

(3) *Second repeat final container test.* If growth appears in any first repeat final container test (thioglycollate or Sabouraud), that test may be repeated provided there was no evidence of growth in any test of the bulk material and material from a sample of twice the number

^{1/}Section 73.73 and all references thereto, revised effective April 12, 1960, 25 FR 3397.

of final containers used in the first test is tested by the same method used in the first test.

(c) *Interpretation of test results.* The results of all tests performed on a lot shall be considered in determining whether or not the lot meets the requirements for sterility, except that tests may be excluded when demonstrated by adequate controls to be invalid. The lot meets the test requirements if no growth appears in the tests prescribed in paragraph (a) of this section. If repeat tests are performed, the lot meets the test requirements if no growth appears in the tests prescribed in paragraph (b) of this section.

(d) *Test samples and volumes—*(1) *Bulk.* Each sample for the bulk sterility test shall be representative of the bulk container material and the volume tested shall be no less than 10 ml. (Note exception in paragraph (f) (9) of this section.)

(2) *Final containers.* The sample for the final container and first repeat final container tests shall be no less than 20 final containers from each filling of each lot, selected to represent all stages of filling from the bulk container. If the amount of material in the final container is 1.0 ml. or less, the entire contents shall be tested. If the amount of material in the final container is more than 1.0 ml., the volume tested shall be the largest single dose recommended by the manufacturer or 1.0 ml., whichever is larger, but no more than 10 ml. of material or the entire contents from a single final container need be tested. (Note exceptions in paragraph (f) (6), (7), (8) and (9) of this section.)

(e) *Culture medium—*(1) *Formulae.* (i) The formula for Fluid Thioglycollate Medium is as follows:

Fluid Thioglycollate Medium

1-cystine.....	0.5 gm.
Sodium chloride.....	2.5 gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$).....	5.5 gm.
Granular agar (less than 15% moisture by weight).	0.75 gm.
Yeast extract (water-soluble)...	5.0 gm.
Pancreatic digest of casein.....	15.0 gm.
Purified water.....	1,000.0 ml.
Sodium thioglycollate (or thio-glycollic acid—0.3 ml.).	0.5 gm.
Resazurin (0.10% solution, freshly prepared).	1.0 ml.
Final pH 7.1 ± 0.1 .	

(ii) The formula for Fluid Sabouraud Medium is as follows:

Fluid Sabouraud Medium

Dextrose	20 gm.
Pancreatic digest of casein.....	5 gm.
Peptic digest of animal tissue.....	5 gm.
Purified water.....	1,000 ml.
Final pH 5.7 ± 0.1 .	

(2) *Culture medium requirements—*(i) *Quality and condition of medium and design of container.* The growth promoting qualities and conditions of the culture medium, and the design of the test container, shall be such as are shown to provide conditions favorable to aerobic and anaerobic growth of microorganisms throughout the test period.

(ii) *Ratio of inoculum to culture medium.* The ratio of the volume of the inoculum to the volume of culture medium shall be such as will dilute the preservative in the inoculum to a level that does not inhibit growth of contaminating microorganisms. Inhibitors or neutralizers of preservative may be considered in determining the proper ratio.

(f) *Exceptions.* Bulk and final container material shall be tested for sterility as described above in this section except as follows:

(1) *Different sterility tests prescribed.* When different sterility tests are prescribed for a product in this part.

(2) *Alternate incubation temperatures.* Two tests may be performed, in all respects as prescribed in paragraph (a) (1) of this section, one test using an incubation temperature of 18° to 22° C., the other test using an incubation temperature of 35° to 37° C., in lieu of performing one test using an incubation temperature of 30° to 32° C.

(3) *Different tests equal or superior.* A different test may be performed provided that prior to the performance of such test a manufacturer submits data which the Surgeon General finds adequate to establish that the different test is equal or superior to the tests described in paragraphs (a) and (b) of this section in detecting contamination and makes the finding a matter of official record.

(4) *Test precluded or not required.* The tests prescribed in this section need not be performed for Whole Blood (Human), Packed Red Blood Cells

(Human), Single Donor Plasma (Human), Smallpox Vaccine and other similar products concerning which the Surgeon General finds that the mode of administration, the method of preparation or the special nature of the product precludes or does not require a sterility test.

(5) *Viscous biological products.* Thioglycollate Broth Medium may be used in lieu of Fluid Thioglycollate Medium to test viscous biological products. The formula for Thioglycollate Broth Medium is as follows:

Thioglycollate Broth Medium. Certain biological products are turbid or otherwise do not lend themselves readily to culturing in Fluid Thioglycollate Medium because of its viscosity. In such instances, the following broth is acceptable in place of the Fluid Thioglycollate Medium, provided it is used in Smith fermentation tubes which have been heated within four hours in a boiling water bath or in free-flowing steam so as to drive the dissolved oxygen out of the medium in the closed arm:

1-cystine.....	0.5 gm.
Sodium chloride.....	2.5 gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$).....	5.5 gm.
Yeast extract (water-soluble)---	5.0 gm.
Pancreatic digest of casein.....	15.0 gm.
Purified water.....	1,000.0 ml.
Sodium thioglycollate (or thio- glycollic acid—0.3 ml.).	0.5 gm.
Final pH 7.1 ± 0.1 .	

(6) *Number of final containers more than 20, less than 200.* If the number of final containers in the filling is more than 20 or less than 200, the sample shall be no less than 10 percent of the containers.

(7) *Number of final containers—20 or less.* If the number of final containers in a filling is 20 or less, the sample shall be two final containers, or the sample need be no more than one final container, provided (i) the bulk material met the sterility test requirements and (ii) after filling, it is demonstrated by testing a simulated sample that all surfaces to which the product was exposed were free of contaminating microorganisms. The simulated sample shall be prepared by rinsing the filling equipment with sterile 1.0 percent peptone solution, pH 7.1 ± 0.1 , which shall be discharged into a final container by the same method used for filling the final containers with the product.

(8) *Samples—large volume of product in final containers.* For Normal Serum Albumin (Human), Normal Human Plasma, Antihemophilic Plasma (Human) and Plasma Protein Solution (Human), when the volume of product in the final container is 50 ml. or more, the final containers selected as the test sample may contain less than the full volume of product in the final containers of the filling from which the sample is taken: *Provided*, That the containers and closures of the sample are identical with those used for the filling to which the test applies and the sample represents all stages of that filling.

(9) *Diagnostic products not intended for injection.* For diagnostic products not intended for injection, (i) only the Thioglycollate Medium test is required, (ii) the volume of material for the bulk test shall be no less than 2.0 ml., and (iii) the sample for the final container test shall be no less than three final containers if the total number filled is 100 or less, and, if greater, one additional container for each additional 50 containers or fraction thereof, but the sample need be no more than 10 containers.

§ 73.74 Purity.

The purity of a product, as defined in § 73.1(r), includes the relative freedom from residual moisture and pyrogenic substances whenever these are factors of significance in the safe use of the product. The relative freedom from residual moisture shall be determined by a procedure which will accurately measure the amount of uncombined water or other volatile liquid present in the finished product. The relative freedom from pyrogenic substances shall be determined by the intravenous injection into normal rabbits of not less than 3.0 ml. per kilo of body weight, following which the thermal response shall not exceed $1.1^\circ C$. More rigid requirements for the pyrogen test shall be observed when the character of the product and the manner of its prophylactic or therapeutic use make this necessary to meet requirements of safety as defined in § 73.1(p).

§ 73.75 Requests for samples and protocols.

Samples of any lot of any licensed product, together with the protocols showing the results of applicable tests, may at any time be required to be sent to the Director, Division of Biologics Standards.

§ 73.76 Ingredients, preservatives, diluents.

All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product shall meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently non-toxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, and in the combination used shall not denature the specific substances in the product below the minimum acceptable potency within the dating period when stored at the recommended temperature.

§ 73.77 Total solids in serums.

Except as otherwise provided by regulation, no liquid serum or antitoxin shall contain more than 20 percent total solids.

§ 73.78 Permissible combinations.

Licensed products may not be combined with other licensed products, either therapeutic, prophylactic or diagnostic, except as a license is obtained for the combined product. Licensed products may not be combined with non-licensable therapeutic, prophylactic, or diagnostic substances except as a license is obtained for such combination.

§ 73.79 Container and closure.

Glass used in the container of a licensed product intended for administration by injection shall be colorless and fully transparent. The quality of the glass and of the closure used shall be such as will not hasten the deterioration of the licensed product or render it less suitable for the use intended within the dating period.

§ 73.80 Standard units or samples.

Standard units or samples for comparison made available by the Institutes

shall be applied in testing for potency all forms of diphtheria antitoxin, tetanus antitoxin, botulism antitoxin Type A, botulism antitoxin Type B, perfringens antitoxin, scarlet fever streptococcus antitoxin, vibron septique antitoxin, anti-pneumococcic serum (Types I, II, V, VII, and VIII), dysentery antitoxin (Shiga), staphylococcus antitoxin, histolyticus antitoxin, oedematiens antitoxin, and sordelli antitoxin and other products for which such units are available.

§ 73.81 Standards of potency; particular products.

Diphtheria antitoxin shall have a potency of not less than 500 units per milliliter. Tetanus antitoxin shall have a potency of not less than 400 units per milliliter. Scarlet fever streptococcus antitoxin shall have a potency of not less than 400 units per milliliter. Antitoxins dispensed in the dried state shall represent liquid antitoxins of not less than these potencies.

§ 73.82 Dating period; date of manufacture.

The dating period shall be determined with reference to the date of manufacture which shall be:

(a) For products for which an official standard of potency exists or which are subject to official potency tests, the last date of satisfactorily passing a potency test;

(b) For products for which no official standard of potency exists or which are not subject to official potency tests,

(1) The date of removal from the animal in case of animal products;

(2) The date of extraction in the case of products used for specific desensitization;

(3) The date of solution in case of venoms,

(4) The date of cessation of growth in case of other products, and

(5) For products which are submitted to the Director, Division of Biologics Standards, for approval prior to release, the date of official release notice.

§ 73.83 Dating period; products in cold storage.

The dating period may be determined with reference to the period of issue

from cold storage: *Provided, That*, except as may be otherwise prescribed for individual products, the date of such issue is not more than six months after the date of manufacture and the product is kept constantly at a temperature not exceeding 10° C., or not more than 1 year after the date of manufacture if the product is kept constantly at a temperature not exceeding 5° C., or not more than 2 years if the product is kept constantly at a temperature not exceeding 0° C.

**ADDITIONAL STANDARDS: TRIVALENT
ORGANIC ARSENICALS**

§ 73.90 Tests prior to release.

Tests required to be made, prior to the release of each lot of a licensed product, shall be supplemented in the case of the trivalent organic arsenicals by tests for:

- (a) Stability,
- (b) Solubility,
- (c) Arsenic content,
- (d) Moisture,
- (e) Relative non-toxicity.

§ 73.91 Pre-testing by Institutes; sample of each lot.

Prior to the release of any lot of the product, the manufacturer shall forward to the Director, Division of Biologics Standards, no less than 15 ampoules of the largest single-dose size in such lot, together with protocols showing the results of each test required prior to release.

§ 73.92 Expiration date.

Notification from the Director, Division of Biologics Standards, that lot samples forwarded in accordance with § 73.91 have satisfactorily passed prescribed tests shall indicate a date which may be taken as the date of manufacture for the purpose of fixing the expiration date. The date of issue shall be the same as the date of manufacture.

§ 73.93 Composition of product.

Solutions or solutions of mixtures in the concentrations recommended for clinical administration shall be of such hydrogen ion value and tonicity as to be physiologically compatible with human blood.

§ 73.94 Container.

The product shall be hermetically sealed under vacuum or under a dry non-oxidizing gas in ampoules prepared from glass of the quality prescribed in § 73.79. The contents of any final container shall not exceed 10 maximum human doses.

§ 73.95 Final container label.

In addition to the labeling requirements stated in § 73.50 the final container label of the trivalent organic arsenicals shall bear the statements required in § 73.96 (b) and (c) and an additional statement giving the amount of the drug contained in the ampoule.

§ 73.96 Outside label.

The outside label, in addition to the complete proper name and all other items required for products generally shall show conspicuously: (a) If the product is dispensed as a mixture or solution, the name of all admixed substances,

(b) If the ampoule is a multiple dose container, the fact that it is a multiple dose container,

(c) Specific method of preparation, if any, required prior to administration, as, for example, alkalization.

**ADDITIONAL STANDARDS: POLIOMYELITIS
VACCINE**

§ 73.100 The product.

(a) *Proper name and definition.* For the purpose of section 351(a)(2) of the Act and § 73.1(k), the proper name of this product shall be "Poliomyelitis Vaccine", which shall consist of an aqueous preparation of poliomyelitis viruses types 1, 2, and 3, grown in monkey kidney tissue cultures, inactivated by a suitable method.

(b) *Strains of virus.* Strains of poliomyelitis virus used in the manufacture of vaccine shall be identified by historical records, infectivity tests and immunological methods. Any strain of virus may be used that produces a vaccine meeting the safety and potency requirements of §§ 73.101, 73.102, and 73.103, but the Surgeon General may from time to time

prohibit the use of any specific strain whenever he finds that it is practicable to use another strain of the same type that is potentially less pathogenic to man and that will produce a vaccine of equivalent safety and potency.

(c) *Monkeys.* Only cynomolgus or rhesus monkeys, or other species of equal suitability, in overt good health that have reacted negatively to tuberculin within two weeks prior to use, shall be used as the source of kidney tissue for the production of virus. Each animal shall be examined at necropsy under the supervision of a qualified pathologist for gross signs of disease and, if there is any gross pathological lesion of significance to their use in the manufacture of the vaccine, the kidneys shall be discarded. Kidney tissue from monkeys that have been used previously for experimental purposes shall not be used, except that monkeys in overt good health, used for the safety or potency tests with negative clinical findings (§§ 73.102 and 73.103) that have reacted negatively to tuberculin prior to such test, may be used within two weeks of the end of the test period.

§ 73.101 Manufacture of poliomyelitis vaccine.

(a) *Cultivation of virus.* Virus for manufacturing vaccine shall be grown with aseptic techniques in monkey kidney cell tissue cultures. Suitable antibiotics in the minimum concentration required may be used. If penicillin is used, not more than 200 units per milliliter may be added.

(b) *Filtration.* Within 72 hours preceding the beginning of inactivation, the virus suspensions shall be filtered or clarified by a method having an efficiency equivalent to that of filtration through an S1 Seitz type filter pad.

(c) *Virus titer.* The 50 percent end-point (TCID₅₀) of the virus fluids after filtration shall be 10⁻⁶ or greater as confirmed by comparison in a simultaneous test (using groups of 10 tubes at 1 log steps or groups of 5 tubes at 0.5 log steps) with a reference virus distributed by the National Institutes of Health. Accept-

able titrations of the reference virus shall not vary more than ± 10 -fold from its labeled titer using 0.5 milliliter inoculum in tissue culture.

(d) *Inactivation of virus.* The virus shall be inactivated, as evidenced by the tests prescribed in § 73.102, through the use of an agent or method which has been demonstrated to the satisfaction of the Surgeon General to be consistently effective in the hands of the manufacturer in inactivating a series of lots of poliomyelitis virus. If formaldehyde is used for inactivation, it shall be added to the virus suspension to a final concentration of U.S.P. solution of formaldehyde of 1:4000, and the inactivation conducted under controlled conditions of pH and time, at a temperature of 36° to 38° C. Three or more virus titers, suitably spaced to indicate rate of inactivation, shall be determined during the inactivation process. Filtration equivalent to that described in paragraph (b) of this section shall be performed after the estimated base-line time (time at which the 50 percent end-point reaches 10° C.), but prior to sampling for the first single strain tissue culture test required in § 73.102(b).

(e) *Additional processing.* Single strain or trivalent pools that have failed to pass safety tests prescribed in § 73.102 (b), (c), or (e) may be treated as follows:

(1) Filtration of clarification by a method having an efficiency equivalent to that of filtration through an S1 Seitz type filter pad.

(2) Negative tests performed as described in § 73.102 (b) and (c) must be obtained on each of two successive samples taken so as to be separated by an interval of at least three days while the material is being subjected to treatment with 1:4000 U.S.P. formaldehyde solution and heat at 36° to 38° C. The first sample may be taken before incubation is begun and the second sample is to be taken after the incubation of at least 3 days is completed. In the case of single strain pools, the volume tested for each tissue culture safety test shall be at least 500 milliliters and in the case of trivalent pools, at least 1,500 milliliters.

(3) Pools which are positive following such additional processing shall not be used for the manufacture of poliomyelitis vaccine.

(f) *Supplemental inactivation.* Supplemental inactivation employing a method capable of reducing the titer of a similarly produced virus suspension by a factor of 10^{-6} may be applied at any point after the filtration step described in paragraph (d) or (e)(1) of this section.

§ 73.102 Tests for safety.

In the manufacture of the product, the following tests relating to safety shall be conducted by the manufacturer.

(a) *The virus pool.* Prior to inactivation each virus pool shall be tested for the presence of B virus and Mycobacterium tuberculosis by suitable animal and culture methods.

(b) *Single strain pool tissue culture tests for poliomyelitis virus.* (1) During inactivation, before pooling to make the final poliomyelitis vaccine, each monovalent bulk strain pool shall be tested for the presence of virus by tissue culture methods. Two samples separated by an interval of at least three days during inactivation at 36° to 38° C. shall be tested.

(2) No less than 500 milliliters of each sample shall be subjected to the complete testing process and each test shall be performed on a different monkey kidney tissue culture cell preparation. Each sample shall be inoculated into five or more tissue culture bottles of a suitable capacity, the ratio of the vaccine to the nutrient fluid being approximately 1:1 to 1:3, and the area of the surface growth of cells being at least 3 square centimeters per milliliter of vaccine. The tissue culture bottles shall be observed at least 14 days.

(3) A first subculture shall be made at the end of seven days from date of inoculation by planting at least 2 percent of the volume from each original bottle into suitable tissue culture containers, followed by refeeding.

(4) A second subculture shall be made from each original bottle in the same manner at the end of 14 days from date of inoculation.

(5) The first and second subcultures shall be each observed for at least seven days.

(6) If cytopathogenic effects occur either in the original bottles of the two tests or in the subcultures from them, or if cellular degeneration appears in the original bottles or in the subcultures before degeneration occurs in uninoculated cultures, the pool shall be held until the matter is resolved. If active poliomyelitis virus is indicated, the strain pool shall not be used for inclusion in a final vaccine unless effectively reprocessed as described in § 73.101(e). If other viruses are present, the pool shall not be used unless it can be demonstrated that such viruses have originated from other than the strain pool being tested.

(c) *Trivalent vaccine pool tissue culture test.* No less than 1,500 milliliters of the trivalent vaccine pool, without final preservative, prepared by pooling the three type pools, each of which has passed all tests described in paragraph (b) of this section, shall be subjected to the complete tissue culture test prescribed in such paragraph in at least two approximately equal tests in separate monkey kidney tissue culture preparations.

(d) *Trivalent vaccine pool lymphocytic choriomeningitis test.* The final vaccine shall be shown to be free of lymphocytic choriomeningitis virus by intracerebral inoculation into 10 or more mice which shall be observed daily for at least 21 days and a negative test shall not be valid unless at least 8 mice survive for this period.

(e) *Final vaccine test for active virus in monkeys.* (1) Vaccine from a sufficient number of final containers selected at random from each filling of each lot shall be pooled to provide a test sample of at least 100 milliliters representing the filling.

(2) Where the number of fillings in a lot is four or more, a test sample from

each filling shall be inoculated into a group of five or more monkeys. Where the number of fillings in a lot is less than four, test samples from the several fillings shall be inoculated into a total of not less than twenty monkeys. A pre-injection serum sample must contain no neutralizing antibody against the three poliomyelitis virus types in a dilution of 1:4 when tested against not more than 1,000 TCID₅₀ doses of virus. At least 80 percent of the test animals representing each filling must survive the test period without significant weight loss, except that if at least 60 percent of the test animals survive the first 48 hours after injection, those animals which do not survive this 48 hour period may be replaced by an equal number of test animals. If less than 60 percent of the test animals survive the first 48 hours, or if less than 80 percent of the animals representing each filling survive the test period without significant weight loss, the test must be repeated.

(3) Vaccine is injected by combined intracerebral, intraspinal, and intramuscular routes into rhesus or cynomolgus monkeys in overt good health, under deep barbiturate anesthesia. The intracerebral injection consists of 0.5 milliliter into the thalamic region of each hemisphere. The intraspinal injection consists of 0.5 milliliter into the lumbar spinal cord enlargement. The intramuscular injection consists of 1.0 milliliter into the right leg muscles. At the same time, an injection of 200 milligrams of cortisone acetate is given into the left leg muscles, and 1.0 milliliter of procaine penicillin (300,000 units) into the right arm muscles. The monkeys are observed for 17 to 19 days and symptoms suggestive of poliomyelitis are recorded.

(4) At the end of the observation period, samples of nervous tissue are taken for virus recovery and identification. Histological sections are prepared from both spinal cord enlargements and examined.

(5) Doubtful histopathological findings necessitate (i) examination of a sample of sections from several regions of the brain in question, and (ii) attempts at virus recovery from the nervous tissues previously removed from the

animal. The test is considered negative if the histological and other studies leave no doubt that poliomyelitis infection did not occur.

§ 73.103 Potency test.

Each lot of vaccine shall be subject to a potency test which permits an estimation of the antigenic capacity of the vaccine. This is done by means of a simultaneous comparison of the antibody levels produced in monkeys by the vaccine under test with the antibody levels of reference serums distributed by the National Institutes of Health. The potency test shall be performed on samples taken after final processing of the trivalent pool including addition of preservative, and shall be conducted as follows:

(a) *Inoculation of monkeys.* A group of 12 or more rhesus or cynomolgus monkeys shall be used. Animals shall weigh between 4 and 8 pounds and shall be in overt good health. Animals that become ill and then remain ill during the course of immunization shall be excluded from the group. The test shall not be valid unless at least 8 survive the test period. The test vaccine shall be given intramuscularly to each monkey in 3 doses of 1.0 milliliter each at seven day intervals. Only undiluted vaccine shall be used.

(b) *Serum samples.* A blood sample shall be taken from each monkey prior to vaccination and then again 7 days after the last injection. Serum shall be separated aseptically, and stored under refrigeration.

(c) *Serum-virus neutralization test.* The titers of individual monkey serums shall be determined in comparison with N.I.H. reference serums in tests designed to include controls for all the variables of significance including the following:

- (1) Serum toxicity control;
- (2) Cell control and cell titration;
- (3) Virus titration control (at least 4 tubes/dilution at $\frac{1}{2}$ log steps); and

(4) Serum controls using type-specific serums to identify the type of virus used in the neutralization test.

(d) *Interpretation of the test.* Animals showing preinoculation titers of $\frac{1}{4}$ or over when tested against not more

than 1,000 TCID₅₀ of virus, shall be excluded from the test. The geometric mean titer of antibody induced in the monkeys surviving the course of immunization and bleeding, shall be calculated. A comparison of the value so obtained shall be made with the values for the reference serums that were tested simultaneously and expressed as ratios between the mean titer values of the serums under test and the mean titer value of the reference serums.

(e) *Potency requirements.* A lot of vaccine tested against National Institutes of Health reference serums IIA, IIA 1/4, and IIA 1/16 shall be satisfactory if the geometric mean value of the group of individual monkey serums representing the lot of vaccine tested is at least 0.86 times the geometric mean value of the three reference serums for type 1, at least 0.75 times for type 2, and at least 0.48 times for type 3. In applying the foregoing requirements, a variation of 66 2/3 percent is acceptable.

§ 73.104 General requirements.

(a) *Final container tests.* Tests shall be made on final containers for identity, safety, and sterility in accordance with §§ 73.72 and 73.73. In addition, the lot shall not be released unless the test for the presence of living poliomyelitis virus described in § 73.102(e) is negative.

(b) *Extraneous protein.* Extraneous protein, capable of producing allergenic effects on injection into human subjects, shall not be added to the final virus production medium. If animal serum is used at any stage, its calculated concentration in the final medium shall not exceed 1:1,000,000.

(c) *Dose.* These additional standards are based on a human dose of 1.0 milliliter for a single injection and a total human immunizing dose of three injections of 1.0 milliliter given at appropriate intervals.

(d) *Labeling.* In addition to compliance with the requirements of §§ 73.50 to 73.55, inclusive, the label or the package enclosure shall include an appropriate statement indicating the type and amounts of antibiotics added, if any. The preservative used shall be stated on the label, as well as allergenic substances

added, if any, and the source, composition and method of inactivation of the viruses.

(e) *Dating.* The expiration date shall be no more than six months after either the date of manufacture as defined in § 73.82(a) or the date of issue from cold storage. Such date of issue shall not be more than six months after such date of manufacture, and the product prior to issue shall be kept constantly at a temperature not exceeding 10° C.

(f) *Requirements for samples and reports.* For each lot of vaccine, the following material shall be submitted to the Director, Division of Biologics Standards, National Institutes of Health, Bethesda 14, Maryland:

(1) A 2,500 milliliter sample, neutralized, not dialyzed, and without final preservative, taken at the latest possible stage of manufacturing before the addition of such preservative.

(2) A 200 milliliter bulk sample of the final vaccine containing final preservative.

(3) A total of not less than 200 milliliter sample of the final vaccine in final labeled containers.

(4) Protocols showing the history of the lot and the results of the tests prescribed in these additional standards.

§ 73.105 Equivalent methods.

Modification of any particular manufacturing method or process or the conditions under which it is conducted as set forth in the additional standards relating to poliomyelitis vaccine (§§ 73.100 to 73.104, inclusive) shall be permitted whenever the manufacturer presents evidence to demonstrate that such modification will provide equal or greater assurances of the safety, purity and potency of the vaccine as the assurances provided by such standards, and the Surgeon General so finds and makes such finding a matter of official record.

(Sec. 215, 58 Stat. 690, as amended; 42 U.S.C. 216. Interprets or applies sec. 351, 58 Stat. 702; 42 U.S.C. 262)

ADDITIONAL STANDARDS: ADENOVIRUS
VACCINE

§ 73.110 The product.

(a) *Proper name and definition.* For the purpose of section 351(a)(2) of the Act and § 73.1(k), the proper name of this product shall be "Adenovirus Vaccine" with a designation of the types of virus included in the vaccine. Such vaccine shall consist of an aqueous preparation of one or more adenoviruses grown in monkey kidney tissue cultures inactivated by a suitable method. Where more than one type of virus is used in the manufacture of the vaccine, equal proportions of each type shall be combined with a tolerance for each component of 5 percent of the total volume.

(b) *Strains of virus.* Strains of adenovirus used in the manufacture of the vaccine shall be identified by historical records, infectivity tests, and immunological methods. Only those strains of virus may be used that (1) produce a vaccine meeting the safety and potency requirements in §§ 73.112 and 73.113, (2) never had any passage in malignant cells of human or animal origin, and (3) have been maintained in monkey kidney cultures for at least 10 passages prior to use.

(c) *Monkey kidney tissue.* Only cynomolgus or rhesus monkeys or other species of equal suitability, in overt good health, that have reacted negatively to tuberculin within 2 weeks prior to use shall be used as a source of kidney tissue for the production of virus. Each animal shall be examined at necropsy under the supervision of a qualified pathologist for gross signs of disease. If there is any gross pathological lesion of any significance to their use in the manufacture of vaccine, the kidneys shall be discarded. Kidney tissue from monkeys that have been used previously for experimental purposes shall not be used, except that monkeys in overt good health, used for the safety or potency tests of adenovirus vaccines with negative clinical findings (§§ 73.112 and 73.113) that have reacted negatively to tuberculin prior to such test, may be used within two weeks of the end of the test period. The monkeys

shall not at any time have been housed in the same building where monkeys actually infected with or exposed to poliovirus are housed, and due precautions shall be taken to prevent cross-infection from any infected or potentially infected monkeys on the premises.

§ 73.111 Manufacture of adenovirus vaccine.

(a) *Cultivation of virus.* Virus for manufacturing vaccine shall be grown with aseptic technique in monkey kidney cell cultures using a synthetic medium. Suitable antibiotics in the minimum concentration required may be used. If penicillin is used, not more than 200 units per milliliter may be added. Phenol red may not exceed a concentration of 0.002 percent.

(b) *Filtration.* Within 72 hours preceding the beginning of inactivation, the virus suspensions shall be filtered or clarified by a method having an efficiency at least equivalent to that of a Selas 02 type filter.

(c) *Virus titer.* The titer of each virus pool after filtration shall be determined by a suitable method. It shall also be demonstrated that each virus pool possesses adenovirus group antigen by the complement-fixing test.

(d) *Inactivation of virus.* The virus shall be inactivated, as evidenced by the test in tissue culture as set forth in § 73.112, through the use of an agent or method which has been demonstrated to be effective in the hands of the manufacturer in inactivating a series of at least 5 consecutive lots of adenovirus vaccine. If formaldehyde is used for inactivation, it shall be added to the virus suspension to a final concentration of U.S.P. formaldehyde solution of at least 1:4000. The inactivation shall be conducted under controlled conditions of pH and time at a temperature of 36° to 38° C. As an indication of inactivation, not less than two samples shall be removed during the inactivation process and treated as prescribed in § 73.112(b)(1). Regardless of the concentration of formaldehyde used, the total heating period shall be not less than 20 hours and at least three times the period required for the reduction of

live virus to a point where no virus is detected in a 5 milliliter sample when tested in accordance with §73.112(b)(1). At the end of the heating period a sample shall be removed for the single strain tissue culture safety test.

§ 73.112 Tests for safety.

In the manufacture of the product, the following tests relating to safety shall be conducted by the manufacturer:

(a) *The virus pool.* (1) Prior to inactivation, each virus pool shall be tested for the presence of B virus and *Mycobacterium tuberculosis* by suitable animal and culture methods;

(2) Each single strain virus pool shall be shown to be free of lymphocytic choriomeningitis virus and other mouse pathogens by intracerebral injection into 10 or more mice which shall be observed daily for at least 21 days. All mice which die during the observation period shall be studied as to the possible cause of death. A negative test shall not be valid unless at least 8 mice survive the full observation period and unless the virus pool was found free of agents pathogenic for mice; and

(3) An identity test shall be done on each virus pool using monovalent adenovirus serums free from poliomyelitis antibodies. Such serums shall have been prepared from animals immunized with virus grown in other than the tissue used for the neutralization test. The identity tests shall be done (i) in monkey kidney and (ii) in HeLa or other equally susceptible cells. The tissue cultures shall be observed for 7 days. Those showing cytopathogenic effect in the presence of type specific serum shall be subcultured in monkey kidney cells or HeLa cells. The subcultures shall be maintained for 7 days and observed for cytopathogenic effect. Only virus pools free of unidentified cytopathogenic agents and free of all viruses pathogenic to man other than adenoviruses may be used for vaccine manufacture.

(b) *Single strain tissue culture test for adenovirus.* (1) The samples specified in § 73.111(d) shall be placed immediately after sampling in contact with sodium bisulfite or a similar formaldehyde neutralizing substance that will

stop the inactivation process. Each sample shall be dialyzed or rendered non-toxic to tissue culture cells by an appropriate method which does not affect the detection of live virus. An amount of fluid representing at least 5 milliliters of the original virus pool shall be inoculated into monkey kidney or other equally susceptible tissue cultures. The tissue cultures shall be maintained for 7 to 12 days and examined at intervals. At the end of the above period, the cell sheet shall be removed from each culture vessel, broken up by an appropriate means, suspended in a portion of its culture fluid equal to at least 10 percent of the volume which was present during incubation, and inoculated into corresponding fresh tissue culture preparations. Any fluids recovered prior to refeeding during original observation period shall be held at 2° to 5° C. A volume of each fluid representing at least 10 percent of the total volume shall be subcultured to fresh tissue culture. All subcultures shall be examined for at least 7 days. This test shall be considered negative only if no cellular degeneration occurs attributable to any virus.

(2) A sample of at least 500 milliliters of each single strain pool shall be fully subjected to the following testing procedure in tissue culture cells, with half the sample in monkey kidney cells and half in suitable human cells of demonstrated high susceptibility to adenovirus and poliovirus. The entire sample shall be dialyzed and rendered non-toxic for tissue culture cells. Each half of the sample shall be inoculated into 4 or more tissue culture bottles of suitable capacity so that direct observation of the culture cells is possible under conditions which assure the growth of adenovirus, poliovirus or simian viruses should infective particles of any one of these viruses be present in the vaccine. The monkey kidney cell cultures shall be performed as described in § 73.102(b) except that a third subculture shall be included after 21 days of incubation of the initial culture and that this subculture shall be made by suspending the cell sheet. The initial human cell cultures shall be observed for at least 12 days. A subculture

shall be made on each fluid at each re-feeding and on the suspension of each cell sheet in the culture fluid removed at the end of the observation period. The inoculum for the subcultures shall be a volume of at least 2 percent of that of the fluid being studied. The subculture shall be examined frequently and refed as required, and maintained for a period of at least 12 days. If a cytopathogenic effect occurs during the test, the vaccine pool shall be held until the matter is resolved. If active poliomyelitis virus or adenovirus is indicated, the strain pool shall not be used for inclusion in a final vaccine. If other viruses are present, the pool shall not be used unless it can be demonstrated that such viruses did not originate from the strain pool being tested.

(c) *Final vaccine pool tissue culture test.* No less than 1,500 milliliters of the final vaccine pool without final preservative, prepared by pooling the individual single strain preparations, shall be tested in accordance with § 73.102 (b) and (c).

(d) *Final vaccine test for active virus in monkeys.* Final bulk vaccine shall be tested in monkeys as prescribed in § 73.102(e) except that the test may be applied to vaccine before it is placed in final containers, and the sample may be dialyzed in order to remove sodium bisulfite or the sodium bisulfite formaldehyde complex before injection intraspinally and intracerebrally into monkeys. In no case, however, shall dialyzed vaccine be used for the intramuscular injection of the monkeys. The test is considered negative if the histological and other studies leave no doubt that virus infections attributable to the vaccine did not occur.

(e) *Exclusion of certain pools from final vaccine.* Pools which fail to pass the tissue culture safety tests prescribed in this section shall not be included in final vaccine, unless it can be clearly shown that the cytopathogenic agent occurred in the test system and not in the vaccine pool. No pool shall be subjected to reprocessing.

§ 73.113 Potency test.

Each lot of vaccine shall be subjected to a potency test which permits an estimation of the antigenic capacity of the vaccine in comparison with a reference vaccine distributed by the National Institutes of Health. This shall be done using at least 6 animals for each dilution of each vaccine tested and measuring the neutralizing antibody response of the animals receiving test vaccine and others receiving reference vaccine in simultaneous tests. The average antibody level for each type shall equal or exceed the corresponding value of the reference vaccine.

§ 73.114 General requirements.

(a) *Separate facilities.* The personnel, equipment and supplies used in the manufacture of adenovirus vaccine shall be separated from personnel, equipment or supplies used in connection with any other pathogenic virus to the extent necessary to prevent cross-contamination.

(b) *Final container tests.* Tests shall be made on final containers for identity, safety, and sterility, in accordance with §§ 73.72 and 73.73.

(c) *Release of vaccine.* A lot of vaccine shall not be released unless all required safety tests have given negative results.

(d) *Extraneous protein.* Extraneous protein capable of producing allergenic effects on human subjects shall not be added to the final virus production medium. If animal serum is used at any stage, its calculated concentration in the final medium shall not exceed 1:1,000,000.

(e) *Nitrogen content.* The final vaccine shall have a protein nitrogen content of less than 0.02 milligram per milliliter.

(f) *Dose.* These additional standards for adenovirus vaccine are based on a human dose not exceeding 1.0 milliliter for a single injection.

(g) *Labelling.* In addition to compliance with the requirements of §§ 73.50 to 73.55, inclusive, the label or package

enclosure shall include an appropriate statement indicating the type and amount of each antibiotic added, if any. The preservative used shall be stated on the label, as well as allergenic substances added, if any, and the source, composition, and method of inactivation of the viruses.

(h) *Dating.* The expiration date shall be not more than 6 months after either the date of manufacture, as defined in § 73.82(a), or the date of issue from cold storage. Such date of issue shall be not more than 6 months after such date of manufacture, and the product prior to issue shall be kept constantly at a temperature not exceeding 10° C.

(i) *Requirements for samples and protocols.* For each lot of vaccine, the following material shall be submitted to the Director, Division of Biologics Standards, National Institutes of Health, Bethesda 14, Maryland:

(1) A 2,500-milliliter sample of the final vaccine taken at the latest possible stage of manufacture before the addition of preservative.

(2) A 200-milliliter bulk sample of the final vaccine containing all preservatives.

(3) A total of at least 200-milliliter sample of the final vaccine in final labelled containers.

(4) Protocol showing the history of the lot and the results of all of the tests which were carried out by the manufacturer.

§ 73.115 Equivalent methods.

The provisions of § 73.105, permitting modifications in methods if found equivalent in assuring safety, purity, and potency, shall be applicable to the additional standards relating to adenovirus vaccine (§§ 73.110 to 73.114, inclusive).

ADDITIONAL STANDARDS: WHOLE BLOOD (HUMAN)

§ 73.300 Proper name and definition.

For the purpose of section 351(a)(2) of the Act and § 73.1(k), the proper name of this product shall be Whole Blood (Human) preceded by a term or terms indicating the anticoagulant used. Whole Blood (Human) is defined as blood collected from human donors for transfusion to human recipients.

§ 73.301 Suitability of donor.

(a) *Method of determining.* The suitability of a donor as a source of Whole Blood (Human) shall be determined by a qualified physician or by persons under his supervision and trained in determining suitability. Such determination shall be made on the day of collection from the donor by means of a medical history, a test for hemoglobin level, and such physical examination as appears necessary.

(b) *Qualifications of donor; general.* Only those persons may serve as a source of Whole Blood (Human) who are in good health, as indicated in part by:

(1) Normal temperature;

(2) Demonstration that systolic and diastolic blood pressures are within normal limits, unless the examining physician is satisfied that an individual with blood pressures outside these limits is an otherwise qualified donor under the provisions of this section;

(3) A blood hemoglobin level which shall be demonstrated to be no less than 12.5 gm. of hemoglobin per 100 ml. of blood;

(4) Freedom from acute respiratory diseases;

(5) Freedom from any infectious skin disease at the site of phlebotomy and from any such disease generalized to such an extent as to create a risk of contamination of the blood; and

(6) Freedom from any disease transmissible by blood transfusion, insofar as can be determined by history and examinations indicated above.

(c) *Additional qualifications of donor; viral hepatitis.* No individual shall be used as a source of Whole Blood (Human) if he has—

(1) A history of viral hepatitis;

(2) A history of close contact within six months of donation with an individual having viral hepatitis;

(3) A history of having received within six months human blood, or any derivative of human blood which the National Institutes of Health has advised the licensed establishment is a possible source of viral hepatitis.

(d) *Therapeutic bleedings.* Blood withdrawn in order to promote the health of a donor otherwise qualified

under the provisions of this section, shall not be used as a source of Whole Blood (Human) unless the container label conspicuously indicates the donor's disease that necessitated withdrawal of blood.

§ 73.302 Collection of the blood.

(a) *Supervision.* Blood shall be drawn from the donor by a qualified physician or under his supervision by assistants trained in the procedure.

(b) *The donor clinic.* The pertinent requirements of § 73.37 shall apply at both the licensed establishment and at any other place where the bleeding is performed.

(c) *Blood containers.* Blood containers and donor sets shall be pyrogen-free, sterile, and identified by lot number. The amount of anticoagulant required for the quantity of blood to be collected shall be in the blood container when it is sterilized.

(d) *The anticoagulant solution.* The anticoagulant solution shall be sterile and pyrogen-free. One of the following formulae may be used in the indicated volumes:

	Solution A	Solution B
Tri-sodium citrate ($\text{Na}_3\text{C}_6\text{H}_5\text{O}_7 \cdot 2\text{H}_2\text{O}$).....	22.0 gm..	13.2 gm.
Citric acid ($\text{C}_6\text{H}_8\text{O}_7 \cdot \text{H}_2\text{O}$).....	8.0 gm...	4.8 gm.
Dextrose ($\text{C}_6\text{H}_{12}\text{O}_6 \cdot \text{H}_2\text{O}$).....	24.5 gm...	14.7 gm.
Water for injection (U.S.P.) to make.....	1,000 ml.	1,000 ml.
Volume per 100 ml. blood.....	15 ml....	25 ml.

No other anticoagulant may be used unless prior to use the Surgeon General has found that under such conditions of dating, storage, and use as he may prescribe, the proposed anticoagulant is at least as effective as the above formulae in preventing coagulation and in preserving red blood cells.

(e) *Donor identification.* Each unit of blood shall be so marked or identified by number or other symbol as to relate it to the individual donor.

(f) *Prevention of contamination of the blood.* The skin of the donor at the site of phlebotomy shall be prepared thoroughly and carefully by a method that gives maximum assurance of a sterile container of blood. The blood shall

be collected by aseptic methods in a sterile system which may be closed or may be vented if the vent protects the blood against contamination.

(g) *Pilot samples for laboratory tests.* Before blood collection, at least one pilot tube shall be attached securely to the container in a manner that will give evidence of removal. The pilot tube and containers for additional samples as needed for laboratory testing shall bear the donor's identification at the time of blood collection. All samples shall be collected by the person collecting the blood at the time of filling the final container.

(h) *Storage.* Immediately after collection, the blood shall be placed in storage at 4° to 6° C. unless it must be transported from the donor clinic to the processing laboratory. In this case the blood shall be placed in temporary storage having sufficient refrigeration capacity to cool the blood continuously toward 4° to 6° C. until it arrives at the processing laboratory where it shall be stored at 4° to 6° C.

§ 73.303 Processing the blood.

All laboratory tests shall be made on a pilot sample specimen of blood taken from the donor at the time of collecting the unit of blood, and these tests shall include the following:

(a) *Serological test for syphilis.* Whole Blood (Human) shall be negative to a serological test for syphilis, except that blood may be issued in an emergency without performing a serological test for syphilis, provided that the label conspicuously indicates that the test was not done.

(b) *Determination of blood group.* Each container of Whole Blood (Human) shall be classified as to ABO blood group. At least two blood group tests shall be made and the unit shall not be issued until grouping tests by different methods or with different lots of anti-serums are in agreement. Only those Anti-A and Anti-B Blood Grouping Serums licensed under, or that otherwise meet the requirements of, the regulations of this part shall be used, and the technique used shall be that for which the serum is specifically designed to be effective.

(c) *Determination of the Rh factors.* Each container of Whole Blood (Human) shall be classified as to Rh type on the basis of tests done on the pilot sample. The label shall indicate the extent of typing and the results of all tests performed. If the test, using Anti-Rh. (Anti-D) Typing Serum, is positive, the container may be labeled "Rh Positive". If this test is negative, the results shall be confirmed by further testing which may include tests for the Rh. variant (D⁺) and for other Rh-Hr factors. Blood may be labeled "Rh Negative" if negative to tests for the Rh. (D) and Rh. variant (D⁺) factors. If the test using Anti-Rh. (Anti-D) Typing Serum is negative, but not tested for the Rh. variant (D⁺), the label must indicate that this test was not done. Only Anti-Rh Typing Serums licensed under, or that otherwise meet the requirements of, the regulations of this part shall be used, and the technique used shall be that for which the serum is specifically designed to be effective.

(d) *Sterility test.* Whole Blood (Human) intended for transfusion shall not be tested for sterility by a method that entails entering the final container.

(e) *Inspection.* Whole Blood (Human) shall be inspected visually during storage and immediately prior to issue. If the color or physical appearance is abnormal or there is any indication or suspicion of microbial contamination the unit of Whole Blood (Human) shall not be issued for transfusion.

§ 73.304 General requirements.

(a) *Manufacturing responsibility.* The entire processing of Whole Blood (Human), including donor examination, blood collection, laboratory tests, labeling, storage and issue, shall be done under the supervision and control of the same licensed establishment except that the Surgeon General may approve arrangements, upon joint request of two or more licensed establishments, which he finds are of such a nature as to assure compliance otherwise with the provisions of this part.

(b) *Periodic check on sterile technique.* One or more containers of blood shall be tested for sterility each month as a continuing check on technique.

(c) *Final container.* The original blood container shall be the final container and shall not be entered prior to issue for any purpose except for blood collection. Such container shall be uncolored and transparent to permit visual inspection of the contents and any closure shall be such as will maintain an hermetic seal and prevent contamination of the contents. The container material shall not interact with the contents under the customary conditions of storage and use, in such a manner as to have an adverse effect upon the safety, purity, or potency of the blood.

(d) *Shipment of Whole Blood (Human).* Whole Blood (Human) shall be maintained continuously at 4° to 10° C. during shipment.

(e) *Reissue of blood.* Blood that has been removed from storage controlled by a licensed establishment shall not be reissued by a licensed establishment unless the following conditions are observed:

(1) The container has a tamper-proof seal when originally issued and this seal remains unbroken;

(2) The original pilot sample is properly attached and has not been removed, except that blood lacking a pilot sample may be reissued in an emergency provided it is accompanied by instructions for sampling and for use within 6 hours after entering the container for sampling;

(3) The blood has been maintained continuously at 4° to 10° C.;

(4) The blood is held for observation until a significant inspection consistent with the requirements of § 73.303(e) can be made.

(f) *Records.* Records shall be maintained of all aspects of the applicable procedures specified in this part.

§ 73.305 Labeling.

In addition to the items required in §§ 73.50, 73.51, 73.52, 73.54, and 73.55 or otherwise by law, the following must appear on the label of each container:

(a) *Anticoagulant. Quantity and*

kind of anticoagulant used and the volume of blood corresponding with the formula prescribed or approved under § 73.302(d).

(b) *Serological test.* The serological test for syphilis used.

(c) *Blood group and type.* Designation of blood group and Rh factors:

(1) The blood group and Rh factors shall be designated conspicuously.

(2) If a color scheme for differentiating the ABO blood groups is used, the color used to designate each blood group on the container shall be:

Blood Group A: Yellow.
Blood Group B: Pink.
Blood Group O: Blue.
Blood Group AB: White.

(d) *Additional information for labels of Group O bloods.* Each Group O blood shall be labeled with a statement indicating whether or not isoagglutinin titers or other tests to exclude so-called "dangerous" Group O bloods were performed, and indicating the classification based on such tests.

§ 73.306 Expiration date.

The expiration date for Citrated Whole Blood (Human) using either of the two anticoagulant formulae specified in § 73.302(d) shall not exceed 21 days after the date of bleeding the donor. The expiration date for Whole Blood (Human) using any other anticoagulant found acceptable under such section shall be determined by the Surgeon General on the basis of the length of red blood cell survival.



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